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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 04/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/979,513	DANIEL ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) *7-8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,9 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ ~~Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)~~ Paper No(s)/Mail Date *702*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed January 13, 2004. Currently, claims 1-10 are pending. Claims 7-8 are withdrawn from prosecution.

Election/Restrictions

2. Applicant's election with traverse of Group I in the paper filed January 13, 2004 is acknowledged.

The response traverses the restriction to Group I and p53. The response argues that each marker bears directly on the treatment profile obtained. This argument has been thoroughly reviewed, but is not found persuasive because the claims are not drawn to a combination which requires all genes. The claims require that the genes are evaluated singly or in various combinations. Thus, minimally the claims require each gene individually.

The response argues that it is irrelevant whether a particular genetic marker is determined by protein or by nucleic acid. This argument has been thoroughly reviewed, but is not found persuasive because protein and nucleic acid expression are not always correlative.

The response traverses the finding of a lack of a special technical feature. The response argues that Tai is not directed to analysis of patients. This argument has been thoroughly reviewed, but is not found persuasive because Tai analyzes tumors from patients (see page 3 of restriction requirement). Further, the claim is not drawn to measuring the effect from a patient. Thus, cell lines would be encompassed by the claims.

The response argues that it is irrelevant that method for detecting different genes are patentably distinct. This argument has been thoroughly reviewed, but is not found persuasive because the effect of chemotherapeutic agents is evaluated with respect to genes.

The requirement is still deemed proper and is therefore made FINAL.

This application contains claims 1-6, in part and 7-8 drawn to an invention nonelected with traverse. A complete reply to the final rejection must include cancellation of nonelected subject matter or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Priority

3. This application claims priority to foreign application Germany 199 22 052.2, filed May 14, 1999.

Should applicant desire to obtain the benefit of foreign priority under 35 U.S.C. 119(a)-(d) prior to declaration of an interference, a translation of the foreign application should be submitted under 37 CFR 1.55 in reply to this action.

Drawings

4. The drawings are acceptable.

Specification

5. The abstract of the disclosure is objected to because the specification is more than 150 words in length. Correction is required. See MPEP § 608.01(b).

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-6, 9-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-6, 9-10 are indefinite because it is unclear how all of the alternative or required steps are related. For example, it is unclear whether the expression profiles are determined in apoptosis regulating or cell growth regulating genes or mutated gene sequences or whether expression is determined for apoptosis regulating or cell growth regulating genes and mutation in genes are determined for analysis. Further, the claim does not clearly provide what the steps of the method require. The claim appears to require a determining step and an association step, however it is unclear how an association is identified, represented and diagnostically evaluated. It is unclear what is meant by represented and whether this may be a mental step or whether the recitation

requires a particular method step. Further, it is unclear what is meant by "diagnostically" evaluated. It is unclear whether the claim requires further method steps or whether the claim completes the method step by merely performing an assay. The metes and bounds of the claimed invention are unclear.

B) Regarding claim 2, 3,5, 6, 9, 10 the phrase "preferably" "particularly" "for example" and "mainly" renders the claims indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

C) Claim 3 is indefinite because it is unclear what is meant by "related to an individually different responsiveness to drugs and are evaluated, particularly with regard to their relevant to the response to therapy." It is unclear what related to an individually different response means. The claim does not appear to clearly set forth any additional steps.

D) Claims 4-6 are indefinite over the recitation "this status" because it is unclear which status is being referred to. Further it is unclear how more efficacious agents are determined. There are no limitations in the claims which illustrate how the determination is made. Therefore, it is unclear how the ordinary artisan would chose more efficacious agents. Moreover, it is unclear what is meant by the status of the genes.

E) Claim 9 depends from Claim 1 which is drawn to a method of detecting the effect of different chemotherapeutic agents and evaluating them. Claim 9, however appears to be drawn to a method of treatment of leukemic diseases by determining the

p53 expression or mutations and where mutations are found, alkylating agents are not administered. It is unclear whether Claim 9 is directed to a method of detecting the effects of chemotherapeutic agents or to a method of selecting/treating with a therapy. Also, it is unclear whether Claim 9 further limits Claim 1.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 1-5, 10 are rejected under 35 U.S.C. 102(a) and 102(e) as being anticipated by Harris et al. (US Pat. 5,985,829, November 1999).

Harris et al. (herein referred to as Harris) teaches methods of screening for compounds capable of inducing apoptosis in certain tumor cells. Harris teaches providing a first cell containing either normal or mutant p53 and the second cell is not capable of undergoing apoptosis. The first and the second cells are contacted with a compound of interest, for example a compound of interest to screen for use as a

chemotherapeutic agent or drug. A comparison of the observations for apoptosis is made, thereby determining whether the compound can induce apoptosis (col. 2, lines 10-30)(limitations of Claim 1, 2, 3, 10). The cells may be malignant, benign or premalignant. The cells may be fibroblastic, epithelial, hematopoietic, breast, ovary, lung, and hematopoietic system (col. 2, lines 38-43)(limitations of claim 5). The screening of large numbers of test compounds is desirable to determine which compounds have the desirable property of inducing apoptosis. Harris teaches using wild type p53 and mutant p53 protein. The method is capable of detecting compounds that have the biological activity of inducing apoptosis in certain cells such as tumor cells having either a wild type of mutant p53 protein (col. 7, lines 10-15). The method can be used for screening large numbers of compounds to identify a group of compounds that are candidate compounds for clinical use and to eliminate from further consideration other compounds which lack activity (col. 7, lines 15-25)(limitations of Claim 4). Harris teaches numerous screening assays which evaluate individual differences in the gene sequence and associations with chemotherapeutics (col. 10-11).

8. Claims 1-6, 10 are rejected under 35 U.S.C. 102(e) as being anticipated by Fung (US Pat. 6,200,810, March 13, 2001).

Fung teaches an assay which compares p53 mutant and wild type p53 with and without treatment with a chemotherapeutic agent. As seen in Figure 14the synthetic p53 mutant induces apoptosis in the lung carcinoma cell line (limitations of Claim 5). Figure 14A shows the wild type p53 without cisplatin; Figure 14B shows the wild type

p53 and cisplatin; Figure 14C shows p4 p53 mutant without cisplatin; Figure 14D shows p4 p53 mutant and cisplatin and Figure 14E and F shows the p5 p53 mutant with and without cisplatin (limitation of Claim 6). As seen in Figure 14, most of the cells that expressed wildtype or p5 mutant p53 underwent apoptosis and disintegrated. However, cells expressing the p4 inactive mutant p53 continued to persist and indeed proliferated to a greater number before treatment (col. 16, lines 5-15). Harris detecting the effect of cisplatin in tumor cells by detecting mutation differences in p53 and the association with cisplatin (limitations of Claim 1, 2, 3). Therefore, treatment of cells containing the p4 mutant with cisplatin would be ineffective (limitations of Claim 4). However treatment of cells containing wild-type and p5 would be effective (limitation of Claim 10).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1-6, 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stoughton et al. (US Pat. 6,370,478, April 2002) in view of Harris et al. (US Pat. 5,985,829, November 1999).

Stoughton et al. (herein referred to as Stoughton) teaches a method for drug interaction prediction using biological response profiles. Stoughton teaches a plurality of cellular constituents in a biological sample is monitored as the sample is subject to various drug treatments. Stoughton teaches the effect of hydroxyurea (hu), a chemotherapeutic agent, in the presence of cyclosporin A (Figure 7). A biological sample is subjected to the treatment of a drug A. A response is calculated based upon the level of cellular constituents before and after treatment of with drug A (col. 2, lines 33-38). The sample is then treated with drug B and measurements are taken. Stoughton teaches that DNA arrays for measuring mRNA level of a large number of genes is particularly preferred (col. 4, lines 43-46).

Stoughton does not specifically teach assaying for p53.

Harris et al. (herein referred to as Harris) teaches methods of screening for compounds capable of inducing apoptosis in certain tumor cells. Harris teaches providing a first cell containing either normal or mutant p53 and the second cell is not capable of undergoing apoptosis. The first and the second cells are contacted with a compound of interest, for example a compound of interest to screen for use as a

chemotherapeutic agent or drug. A comparison of the observations for apoptosis is made, thereby determining whether the compound can induce apoptosis (col. 2, lines 10-30)(limitations of Claim 1, 2, 3, 10). The cells may be malignant, benign or premalignant. The cells may be fibroblastic, epithelial, hematopoietic, breast, ovary, lung, and hematopoietic system (col. 2, lines 38-43)(limitations of claim 5). The screening of large numbers of test compounds is desirable to determine which compounds have the desirable property of inducing apoptosis. Harris teaches using wild type p53 and mutant p53 protein. The method is capable of detecting compounds that have the biological activity of inducing apoptosis in certain cells such as tumor cells having either a wild type of mutant p53 protein (col. 7, lines 10-15). The method can be used for screening large numbers of compounds to identify a group of compounds that are candidate compounds for clinical use and to eliminate from further consideration other compounds which lack activity (col. 7, lines 15-25)(limitations of Claim 4). Harris teaches numerous screening assays which evaluate individual differences in the gene sequence and associations with chemotherapeutics (col. 10-11).

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified the DNA array of Stoughton to include p53 which is known to be associated with resistance and sensitivity to compounds. The ordinary artisan would be motivated to have included well known tumor suppressor genes, apoptosis genes and other known cancer genes upon the DNA array of Stoughton to evaluate the expression and effect of various compounds upon the genes

to enable a method of screening for effects of various compounds on gene expression or mutations within genes as taught by Harris.

11. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Spengler (US Pat. 5,876,972, March 1999).

It is noted that while the Claim depends from Claim 1, the claim does not appear to further limit Claim 1.

Spengler et al. (herein referred to as Spengler) teaches that cells lacking wild-type p53 are resistant to agents including fluorouracil, duxrubicin, etoposide which are alkylating agents. Whereas cells expressing wild-type p53 are sensitive to them and undergo cell death by apoptosis. Spengler teaches that p53 mutations dramatically reduce the probability that patients with B cell chronic lympocyte leukemia will enter remission after chemotherapy (col. 13, lines 60-65). Spengler teaches that the evaluation of the status of nucleic acids could serve as an decisive parameter for the extent and necessity of surgical resection and the need for adjuvant therapy.

Spengler does not specifically teach a method of treatment of CLL however, Spengler specifically teaches that cells expression wild-type p53 are sensitive to alkylating agents and allows cell death. However, cells that lack wild-type p53 are resistant to alkylating agents. Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have avoided administration of alkylating agents to individuals who were resistant to the agents. The ordinary artisan would not have been motivated to have administered a agent which was predictively not

going to be effective for inducing apoptosis to a patient. Therefore, the ordinary artisan would have been motivated to have avoided administering an alkylating agent to an individual with mutant p53 and would have selected a different therapy.

Conclusion

12. No claims allowable over the art.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272-0745.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

J. Goldberg

Jeanine Goldberg
Patent Examiner
April 1, 2004